

Temporal pole morphology in first-episode schizophrenia patients:: Clinical correlations

Roberto Roiz-Santiañez, Rocío Pérez-Iglesias, Carlos Quintero, Diana Tordesillas-Gutiérrez, Ignacio Mata, Agustín Gutiérrez, Elena Sánchez, Angel Pazos, Rafael Tabarés-Seisdedos, José Luis Vázquez-Barquero, Benedicto Crespo-Facorro

1. Introduction

The temporal pole (TP), located in the anterior tip of the temporal lobe, is a component of the paralimbic circuit along with the orbitofrontal cortex and the insular cortex (Mesulam and Mufson, 1982). The TP has been considered to be engaged in various cognitive functions and has been thought to play a role in affectional–sensory integration (Nakamura and Kubota, 1996; Gloor, 1997; Mesulam, 2000). Neuroimaging investigations have shown that the pathological process in schizophrenia predominantly affects the fronto–temporolimbic–paralimbic regions (Takahashi et al., 2009). Nonetheless, neuroimaging studies of the TP in schizophrenia patients have shown inconsistent results. Kasai et al. (2003), using a region of interest (ROI) approach, reported a significant graymatter volume reduction in the left TP in first-episode schizophrenia patients. Inconsistently, Witthaus et al. (2009), using voxel-based morphometry methodology, reported a significant reduction in the right TP in first-episode patients, failing to find differences in the left side. Investigations of chronic schizophrenia patients have also shown inconsistencies. Thus, some studies have reported a significant reduction in bilateral TP gray matter volume (Wright et al., 1999; Gur et al., 2000). On the other hand, in a previous study (Crespo-Facorro et al., 2004), we failed to find any morphological abnormality in the TP in a sample of males with schizophrenia, although a significant association between TP volume and clinical measures was found. Further studies using large samples and anatomically defined ROIs are needed to clarify these inconsistencies. We aimed, using an ROI approach, (1) to investigate TP gray matter volume and cortical surface area anomalies in first-episode schizophrenia patients; (2) to investigate whether these morphometric anomalies may significantly influence clinical features of the illness.

2. Method

2.1. Subjects

Patients were drawn from a large prospective longitudinal study on first-episode psychosis (PAFIP) conducted at the University Hospital Marqués de Valdecilla, Santander, Spain. It conformed to international standards for research ethics and was approved by the local institutional review board. Only those patients (80) with a DSMIV diagnosis of schizophrenia 6 months after inclusion entered this study. The diagnoses were confirmed using the Structured Clinical Interview for DSM-IV (SCID-I) (First et al., 2001). Our operational definition for a “first episode of psychosis” included individuals with a non-affective psychotic episode who have not received previously antipsychotic treatment regardless of the duration of psychosis. Mean age at onset was 29.29 years (S.D.=8.82).

Forty-eight (60%) of the patients were males. The mean duration of psychosis at intake was 17.75 months (S.D.=35.83). At the time of brain magnetic resonance imaging (MRI), 14 were taking a conventional antipsychotic (haloperidol) and 66 patients were on atypical antipsychotics (14 olanzapine, 13 risperidone, 15 quetiapine, 14 ziprasidone and 10 aripiprazol). Mean time from first antipsychotic treatment to scan date was 4.39 weeks (S.D.=3.65). In addition, a sample of 82 healthy control subjects (52 male subjects, 30 female subjects) was included in this study. They were recruited from the community through advertisements. Mean age at time of MRI scan was 27.56 years (S.D.=7.62).

2.2. Clinical assessments

Clinical symptoms were rated using the Brief Psychiatric Rating Scale (BPRS) total ([Overall and Gorman, 1962](#)), the Scale for the Assessment of Negative Symptoms (SANS) ([Andreasen, 1983](#)) and the Scale for the Assessment of Positive Symptoms (SAPS) ([Andreasen, 1984](#)). We also divided psychopathology into three dimensions of symptoms (psychotic, negative, and disorganized). Handedness was assessed by the Edinburgh Inventory ([Oldfield, 1971](#)). Duration of untreated illness (DUI) was defined as the time from the first unspecific symptoms related to psychosis (for such symptom to be considered, there should be no return to previous stable level of functioning) to initiation of adequate antipsychotic drug treatment. Duration of untreated psychosis (DUP) was defined as the time from the first continuous (present most of the time) psychotic symptom to initiation of adequate antipsychotic drug treatment. Duration of prodromal period (DPP) was defined as the period from the first unspecific symptoms related to psychosis (as defined above) to the first continuous (present most of the time) psychotic symptom.

2.3. MRI acquisition and image processing

All multi-modal MRI scans were obtained at the University Hospital of Cantabria using a 1.5 Tesla General Electric SIGNA System (GE Medical Systems, Milwaukee, WI). Three-dimensional T1-weighted images and two-dimensional PD and T2 sequences were acquired. Imaging parameters have been previously described ([Crespo-Facorro et al., 2007](#)). Images were processed using the software BRAINS2 ([Andreasen et al., 1996](#); [Magnotta et al., 2002](#)). In short, T1-weighted images were spatially normalized and resampled to 1.0-mm³ voxels. T2- and PD-weighted images were aligned to the spatially normalized T1-weighted image. In order to classify volumes into gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF), the data sets were segmented by using the multispectral data and a discriminant analysis method based on automated training class selection ([Harris et al., 1999](#)). The tissue-classified image was then used to generate a triangle-based iso-surface with a threshold of 130 representing pure gray matter, which corresponds to the parametric center of the cortex and serves as a useful estimate of its physical center ([Magnotta et al., 1999](#)). Hand-traced ROIs were used to surround contiguous areas of the gray matter triangle iso-surface.

On each two-dimensional (2D) slice, the cortical surface is visualized as a continuous contour that represents the intersection between the 2D plane and the three-dimensional (3D) triangulated surface. The surface area was measured by summing areas of all triangles within the tracings that were made to define the TP. The TP was manually outlined without knowledge of the diagnosis using a previously published method (Crespo-Facorro et al., 2000; Kim et al., 2000). The posterior border of the temporal pole has been defined according to previous articles describing the definition of the temporal pole using MRI, and it is defined by the coronal plane where there is no frontotemporal junction (Gur et al., 2000; Crespo-Facorro et al., 2000; Kim et al., 2000). Since the lateral, medial, anterior, superior, and inferior boundaries of the TP are defined by the natural limits of the temporal lobe anterior to the frontotemporal junction, tracings are simply done by including all triangulated surface lines reflecting the temporal cortex. Moving rostrally, tracing is continued until the triangular surface disappears. The reliability study for this method was performed on a set of 10 MRI scans by two raters (D.T. and C.Q.) using the original tracing from Crespo-Facorro et al. (2000) as gold standard. The intra-class r coefficients were $r=0.96$ for TP gray matter volumes and $r=0.94$ for the TP surface area.

2.4. Statistical analysis

All statistical analyses were performed with the Statistical Program for the Social Sciences (SPSS). To examine differences in ROIs, a repeated measures analysis of covariance (ANCOVA) was performed, with side (left or right) as the within-subjects factor and group (patient, control) and gender as the between-subjects factors. For volume measures, the covariates were intracranial volume and age; for surface area measures, the covariates were total cortical surface area and age. Cohen's d is provided to estimate the magnitude of the differences between groups. Similar analyses (excluding gender as between-factor) were conducted for both males and females independently. All the outliers (defined as 3 S.D. above or below the mean) were excluded from the analyses. Because clinical assessment scores were not normally distributed, Spearman's correlation coefficients were calculated to examine the relationships between TP gray matter volume and clinical variables.

3. Results

A significant difference between groups was found for age ($F=6.79$; $P=0.010$). There were no significant differences between groups with regard to gender, laterality, intracranial volume, cortical surface area, parental socioeconomic status, alcohol or cannabis use (all $P>0.210$). These data are available upon request. No significant differences were found between patients and control subjects in any of the TP measurements (Table 1). There were neither significant group-by-side ($P>0.719$) nor group-by-gender interactions ($P>0.191$). When males and females were analyzed separately, the results remained unchanged ($P>0.100$). There were no significant correlations between clinical variables (psychotic, negative and disorganized symptom dimensions) and TP gray matter volumes ($P>0.356$; all $|r|<0.11$).

No significant associations were seen between duration of untreated illness, duration of untreated psychosis, duration of prodromal period and TP gray matter volumes (PN0.213; all $|r| < 0.14$). Results remained the same when IQ was introduced as a covariate.

4. Discussion

In a representative sample of patients with a first-episode of schizophrenia, we found that first-episode schizophrenia patients did not show anomalies in TP gray matter volume and cortical surface area measurements compared with healthy volunteers; TP morphological variables were not associated with clinical variables. In first-episode patients, [Kasai et al. \(2003\)](#), using an ROI approach, described a reduction in left TP gray matter volume without a gender effect in a sample of schizophrenia patients (N=27) who had been minimally treated (median of 1 month). [Witthaus et al. \(2009\)](#), using voxel-based morphometry, recently reported a significant reduction in the right TP, but not in the left side, in a sample of 23 first-episode schizophrenia patients (17 drug naïve patients). Our results reported herein failed to replicate these TP morphological anomalies in first-episode patients. In a previous article we consistently observed no differences in TP morphometry in right-handed male chronic schizophrenia patients using the same methodology ([Crespo-Facorro et al., 2004](#)). Interestingly, when we analyzed the subsample of righthanded male first-episode patients, neither did we find significance differences between patients and healthy subjects (P's N0.100). In addition, we failed to observe significant differences in the hemispheric asymmetry of TP measurements in chronic patients ([Crespo-Facorro et al., 2004](#)). In the same way, we did not find a significant group \times side interaction (which is used to measure hemispheric asymmetries) for TP measurements in first-episode patients. Investigations reported to date have failed to provide a consistent description of the TP anomalies present in schizophrenia. Small sample sizes, lack of representativeness of their samples, differences in gender distribution and the effect of confounding factors such as alcohol, tobacco and cannabis consumption may account for discrepancies between investigations. In addition, differences in the methodology (field strength, scanner manufacturer, imaging magnetic gradients, software package and version, or the parameters used in the analysis) may also account for inconsistencies between studies ([Jovicich et al., 2009](#)). The clinical implications of TP anomalies in schizophrenia have not been clearly established. Our results support the hypothesis that TP gray matter volume is not correlated with clinical variables. Similarly, other studies ([Gur et al., 2000](#); [Kasai et al., 2003](#)) did not find an association between TP volume and clinical measures. However, in chronic schizophrenia, there was a significant association between a reduction in the TP volume and the severity of disorganized and psychotic symptoms ([Crespo-Facorro et al., 2004](#)). Further investigations are warranted to confirm the functional implications of the TP in the pathophysiology of schizophrenia. In summary, our findings, based on a large and representative sample of first-episode schizophrenia patients, do not confirm the presence of significant TP morphometric anomalies. Neither did we observe associations between TP gray matter volume and clinical measures.

